Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) as second-line therapy in metastatic colorectal cancer: a randomized phase III noninferiority study

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Background: To demonstrate the noninferiority of capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/folinic acid and oxaliplatin (FOLFOX-4) as second-line therapy in patients with metastatic colorectal cancer after prior irinotecan-based chemotherapy.

Patients and methods: A total of 627 patients were randomly assigned to receive XELOX (n = 313) or FOLFOX-4 (n = 314) following disease progression/recurrence or intolerance to irinotecan-based chemotherapy. The primary end point was progression-free survival (PFS).

Results: PFS for XELOX was noninferior to FOLFOX-4 [hazard ratio (HR) = 0.97; 95% confidence interval (CI) 0.83–1.14] in the intention-to-treat (ITT) population. Median PFS was 4.7 months with XELOX versus 4.8 months with FOLFOX-4. The robustness of the primary analysis was supported by multivariate and subgroup analyses. Median overall survival in the ITT population was 11.9 months with XELOX versus 12.5 months with FOLFOX-4 (HR = 1.02; 95% CI 0.86–1.21). Treatment-related grade 3/4 adverse events occurred in 50% of XELOX- and 65% of FOLFOX-4-treated patients. Whereas grade 3/4 neutropenia (35% versus 5% with XELOX) and febrile neutropenia (4% versus <1%) were more common with FOLFOX-4, grade 3/4 diarrhea (19% versus 5% with FOLFOX-4) and grade 3 hand–foot syndrome (4% versus <1%) were more common with XELOX.

Conclusion: XELOX is noninferior to FOLFOX-4 when administered as second-line treatment in patients with metastatic colorectal cancer.

Key words: capecitabine, 5-fluorouracil/folinic acid, FOLFOX-4, metastatic colorectal cancer, oxaliplatin, XELOX

introduction

Combinations of 5-fluorouracil/folinic acid (5-FU/FA) and either irinotecan (e.g. FOLFIRI, Douillard, AIO regimens) or oxaliplatin (e.g. FOLFOX-4, FOLFOX-6 regimens) are established standard regimens for the first-line treatment of metastatic colorectal cancer [1]. The choice of second-line therapy for patients whose disease progresses or recurs is influenced by the prior first-line regimen. Patients who are initially treated with an irinotecan-based regimen tend to be offered an oxaliplatin-based regimen as second-line therapy and vice versa.

Capecitabine (Xeloda®; Hoffmann-La Roche Inc., Nutley, NJ) is an oral fluoropyrimidine that has similar efficacy to bolus 5-FU/FA in both the first-line treatment of metastatic colorectal cancer [2–4] and as adjuvant therapy for stage III colon cancer [5]. Capecitabine has been evaluated in combination with oxaliplatin in a variety of different schedules [6–8]. XELOX, a regimen combining capecitabine and oxaliplatin, consists of the standard 21-day intermittent schedule (i.e. 14 days on followed by 7 days off) of capecitabine combined with oxaliplatin on day 1. XELOX has emerged as a viable treatment option in both the first-line [6, 9, 10] and second-line settings [11, 12]. Noninferiority of XELOX versus FOLFOX has recently been demonstrated in two phase III studies in the first-line treatment of metastatic colorectal cancer [13, 14].

The present phase III trial (NO16967) was conducted to establish the noninferiority of XELOX versus FOLFOX-4 in patients with metastatic colorectal cancer with progressive...
disease during or shortly following first-line therapy with an irinotecan-based regimen.

patients and methods

study design

The primary objective of this randomized, phase III study was to demonstrate that XELOX was noninferior to FOLFOX-4 in terms of progression-free survival (PPS) in patients with metastatic colorectal cancer who had previously received first-line therapy with an irinotecan-based regimen. The study was open label because of the different routes of administration of the fluoropyrimidine components of these regimens.

The study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Written informed consent was obtained from all patients participating in the study. Approval of the protocol was obtained from an Independent Ethics Committee or Institutional Review Board.

patient population

Outpatients with histologically confirmed colorectal cancer that was metastatic and had progressed during or within 6 months after first-line chemotherapy for metastatic disease with an irinotecan-based regimen (i.e. irinotecan plus 5-FU/FA or irinotecan, 5-FU/FA and a targeted biological agent) were enrolled. Patients who had stopped first-line therapy within the first 8 weeks because of toxicity were also eligible. Patients may not have received any chemotherapy for at least 3 weeks before randomization. Prior radiotherapy was permitted providing that it did not involve target lesions (unless progression of these lesions was documented) and had been completed at least 4 weeks before randomization.

Patients had to be ≥18 years of age, have an Eastern Cooperative Oncology Group (ECOG) performance status of two or less and a life expectancy of >3 months. All patients had to have at least one unidimensionally measurable lesion with a diameter of >20 mm on conventional computed tomography (CT) or magnetic resonance imaging (MRI) scans or >10 mm on spiral CT or MRI scans. Patients had to have adequate hematological, hepatic and renal function. Pregnant or breast-feeding women were excluded. Other key exclusion criteria were prior treatment with oxaliplatin, clinically significant cardiac disease and central nervous system metastases.

treatment plan

Dynamic randomization was used to assign patients to treatment. Randomization was stratified by geographic region (Oceania, Central Asia, Eastern Asia, South Africa, Canada, United States, Israel, Mexico, South America, Northern Europe, Southern Europe, Eastern Europe, Central Europe, United Kingdom, Italy and France); ECOG performance status (0 versus 1 or 2), number of metastatic sites (organs) at baseline (1 versus >1), alkaline phosphatase level at baseline (normal versus above normal) and reason for termination of prior irinotecan-based therapy (tumor progression versus toxicity).

XELOX consisted of a 2-h i.v. infusion of oxaliplatin 130 mg/m² on day 1 plus oral capecitabine 1000 mg/m² twice daily on days 1–15 of a 3-week cycle administered on an outpatient basis. The first dose of capecitabine was given on the evening of day 1 and the last dose on the morning of day 15 (28 doses/cycle). Capecitabine compliance was monitored by counting any returned tablets at the start of each cycle. The FOLFOX-4 regimen was administered as previously described [15].

Patients could receive a total of 24 weeks of treatment (study treatment phase) and, in the absence of progression, could receive treatment beyond week 24 in a poststudy treatment phase. Treatment was continued until disease progression, intolerable adverse events or patient refusal to continue. Patients whose disease became operable were withdrawn from the study treatment phase but could continue in the poststudy treatment phase. Capecitabine or 5-FU/FA monotherapy was permitted in the event of discontinuation of oxaliplatin because of toxicity. Standard dose or schedule modifications of capecitabine, 5-FU and oxaliplatin were carried out in patients experiencing treatment-related toxicity as per the study protocol. Patients with documented progressive disease could be offered third-line treatment at the treating physician’s discretion.

assessments

Demographic data, medical history, physical examination, chest X-ray, ECG, and carcinoembryonic antigen (CEA) levels were assessed within 21 days before starting treatment. Vital signs, ECOG performance status, height, weight, hematology and blood chemistry were carried out within 7 days before starting treatment. During treatment, a physical examination and hematologic/biochemistry analyses were repeated on day 1 of every treatment cycle.

Tumor assessments, using MRI, CT scan or X-ray, were made within 28 days before starting study treatment. Assessments were then repeated using the same imaging technique approximately every 6 weeks and again within 2 weeks of study completion, withdrawal or treatment discontinuation. Response evaluation criteria in solid tumors guidelines [16] were used to define all responses. Confirmation of response was required after a minimum of 4 weeks. Assessments of tumor response were made by investigators and also by an independent response review committee (IRC) that was blinded to treatment assignment. After completion of study treatment, patients were followed up every 3 months until disease progression or death.

Patients were evaluated for adverse events during therapy and until 28 days after the last study drug dose. Adverse events were graded according to National Cancer Institute—Common Terminology Criteria for Adverse Events, version 3.

statistical analysis

The intention-to-treat (ITT) patient population included all patients who underwent randomization. At the request of regulatory authorities, the per-protocol (PP) population was defined as the ITT population minus patients considered to have major violations of inclusion or exclusion criteria and patients who did not receive at least two cycles of XELOX or three cycles of FOLFOX-4 for reasons other than progressive disease. The safety population was defined as all patients receiving at least one dose of study drug. PFS was the primary endpoint of the study and was defined as the time from the date of randomization to the first documentation of disease progression by the investigators or death from any cause. Noninferiority of XELOX versus FOLFOX-4 was concluded if the upper limit of the two-sided 95% confidence interval (CI) for the hazard ratio (HR) of PFS did not exceed 1.30. Planned multivariate analyses of PFS were carried out by multiple Cox regression analyses using potential prognostic factors (i.e. gender, age, time from diagnosis to recurrence and baseline CEA level), stratification variables and geographic region. Subgroup analyses of PFS were also prospectively planned.

The secondary efficacy end points were overall survival (OS), overall response rate (ORR), time to response, duration of response and time to treatment failure (defined as time from date of randomization to the first documentation of insufficient response, death from any cause, adverse events, failure to return, refusal of treatment or withdrawal of consent). PFS, OS, duration of response and time to treatment failure were summarized as Kaplan–Meier estimates, together with HRs and 95% CIs.

Using a noninferiority margin of 1.30, which corresponded to retention of at least 50% of the benefit that oxaliplatin plus 5-FU/FA has shown over 5-FU/FA alone, it was estimated that a total of 610 patients needed to be randomized to achieve 80% statistical power in an analysis of the PP population.
results

patient population

From July 2003 to May 2005, a total of 627 patients from 87 centers in 19 countries were enrolled in the study. All 627 patients were randomized to receive either XELOX (313 patients) or FOLFOX-4 (314 patients) and made up the ITT population. A total of 503 patients were included in the PP population: 252 patients in the FOLFOX-4 group and 251 patients in the XELOX group. The most common reason for exclusion was that fewer than two XELOX or three FOLFOX-4 cycles of therapy had been administered for reasons other than progressive disease or death (51 patients in the FOLFOX-4 group and 42 patients in the XELOX group) (Figure 1).

Baseline demographic and clinical characteristics were well balanced between treatment arms (Table 1). Most patients had baseline ECOG scores of zero or one (>90% in both treatment groups). All patients had previously received irinotecan in combination with 5-FU with or without FA. Thirteen patients (2%) had received bevacizumab.

treatment exposure and withdrawals

The median number of cycles of study treatment given was 6 (range 1–8) in the XELOX group and 8.5 (range 1–12) in the FOLFOX-4 group; the median duration of treatment was 3.9 (range 0–8.1) months in the XELOX group and 3.9 (range 0–8.0) months in the FOLFOX-4 group. A similar proportion of patients in each treatment group (33% in XELOX and 31% in FOLFOX-4) completed 24 weeks of treatment (i.e. eight cycles of XELOX and 12 cycles of FOLFOX-4). The median dose intensities (i.e. ratio of doses received to doses planned) were similar for both fluoropyrimidines (0.99 for 5-FU, 0.93 for capecitabine) and identical for oxaliplatin (0.99) in XELOX and FOLFOX-4.

During study treatment, more patients in the FOLFOX-4 group \( (n = 143; 46\%) \) than in the XELOX group \( (n = 117; 38\%) \) withdrew because of progressive disease, whereas more patients in the XELOX group withdrew because of adverse events \( (n = 64; 21\%) \) versus \( n = 42; 14\% \) with FOLFOX-4).

efficacy

The results of the efficacy analysis are presented in Table 2. The cut-off date for PFS was 31 August 2006 when at least 458 progression or death events were expected in the PP population. The median duration of follow-up at the clinical cut-off date was 25.7 months.

The primary objective of the study—the determination of the noninferiority of XELOX compared with FOLFOX-4 in terms of PFS—was met. XELOX was noninferior to FOLFOX-4 with a progression HR of 0.97 (95% CI 0.83–1.14) in the ITT (Figure 2A) and 1.04 (95% CI 0.87–1.24) in the PP populations. The upper limit of the 95% CI was below the predefined noninferiority margin of 1.30 in both ITT and PP populations. Median PFS was 4.7 months with XELOX versus 4.8 months with FOLFOX-4 in the ITT population and 3.1 months with XELOX versus 3.5 months with FOLFOX-4 in the PP population.

Median OS in the ITT population was 11.9 months with XELOX versus 12.5 months with FOLFOX-4 with a HR of 1.02 (95% CI 0.86–1.21) (Figure 2B). In the PP population, median

Figure 1. CONSORT diagram.
OS was 12.9 months with XELOX versus 13.2 months with FOLFOX-4; the HR was 1.05 (95% CI 0.88–1.27).

ORR in the ITT population was similar in both the XELOX and FOLFOX-4 treatment groups as assessed by either the investigators or the IRC (Table 2). The ORR as assessed by investigators was 20% in the XELOX group and 18% in the FOLFOX-4 group. The ORR as assessed by the IRC was 15% in the XELOX group and 12% in the FOLFOX-4 group.

A similar proportion of patients in the two treatment groups received further anticancer therapy after discontinuing study treatment (60% with XELOX and 62% with FOLFOX-4), including drug therapy, surgery and radiotherapy. The most commonly used treatments were 5-FU (25% in the XELOX group versus 25% in the FOLFOX-4 group), capcitabine (10% versus 26%), irinotecan (16% versus 21%), cetuximab (15% versus 19%), oxaliplatin (17% versus 14%), radiotherapy (18% versus 14%) and bevacizumab (6% versus 7%). In general, the use of medications was well balanced between treatment groups, except that capcitabine and irinotecan were used less frequently in the XELOX group than in the FOLFOX-4 group.

Multivariate analyses
Multivariate analyses incorporating prespecified prognostic factors (i.e. key demographic and baseline variables, stratification variables and geographic region) supported the results of the primary unadjusted analysis of PFS.

Subgroup analyses
Subgroup analysis of PFS in the ITT population according to demographic and baseline variables, stratification variables and geographic region were consistent with the primary analysis. The 95% CI for the HRs for each subgroup included 1.00 (Figure 3).

Safety
A summary of the most frequently reported (>15% of patients) adverse events is presented in Table 3. Treatment-related grade 3/4 adverse events were more frequent with FOLFOX-4 than with XELOX (65% versus 50%), as were grade 4 events (18% versus 3%), these differences being mainly due to higher occurrence of grade 3/4 neutropenia in the FOLFOX-4 group. Febrile neutropenia occurred in 4% of FOLFOX-4 recipients and <1% of XELOX recipients.

Grade 3/4 gastrointestinal disorders were more common in the XELOX group (33% versus 20%), mainly due to grade 3 diarrhea (19% versus 5%). All-grade (23% versus 6%) and grade 3 (4% versus <1%) hand–foot syndrome were more common in the XELOX group (25% versus 25%), mainly due to grade 3 hand–foot syndrome (19% versus 1%).
common in the XELOX group compared with the FOLFOX-4 group. The incidence of neurosensory toxicity was similar in both the XELOX and FOLFOX-4 groups (grade 3/4 events 9% versus 8%). Grade 3/4 cardiac adverse events were rare (0.6% in both treatment arms).

Treatment-related mortality up to 28 days after the last dose was 1% in both treatment arms. All-cause 60-day mortality was 4% in both treatment arms.

discussion

This phase III randomized trial showed that XELOX is noninferior to FOLFOX-4 with respect to PFS when given as second-line therapy in patients with metastatic colorectal cancer following treatment with irinotecan-based chemotherapy. Although the study was not powered for an analysis of OS, the OS data were supportive of the primary analysis. The findings were further reinforced by predefined multivariate and subgroup analyses. HRs adjusted for prespecified covariates were similar to the unadjusted HR of the primary analysis, showing that the conclusions are robust and are not dependent upon selected prognostic factors or geographic region.

The finding of noninferiority of the XELOX regimen versus FOLFOX-4 is consistent with recently completed phase III trials in the first-line setting [13, 14]. In the multinational XELOX-1 (NO16966) study, which involved almost 1000 patients in each treatment arm, noninferiority of XELOX with or without bevacizumab was demonstrated versus FOLFOX-4 with or without bevacizumab [13]. Dureux et al. [14] showed in a smaller French phase III study (n = 306) that XELOX and FOLFOX-6 were at least equivalent in terms of ORR, the primary study end point.

In the present study, ORRs were similar in the XELOX and FOLFOX-4 groups on the basis of the investigators’ assessments. An independent review of tumor assessments confirmed the similarity of response rates in the XELOX and FOLFOX-4 groups. Similar results for both regimens were also observed for the time to response and time to treatment failure.

The results documented with the FOLFOX-4 regimen in our trial are consistent with those of other trials carried out in the...
second-line setting. Data from the GERCOR V308 and EFC4584 trials [17–19] reported ORRs of 10% and 15% with FOLFOX-4 or FOLFOX-6 as confirmed by independent external review compared with an IRC-assessed ORR of 12% in the present study. Median PFS of 4.5 and 5.6 months in previous studies [17–19] were also very similar to the median value of 4.8 months reported in the present study.

It is also interesting to note that our results are consistent with those of a Nordic phase II study, which evaluated the efficacy of XELOX as second-line therapy following treatment failure with irinotecan-based chemotherapy in 70 patients with advanced colorectal cancer [11]. The authors reported an investigator-assessed ORR of 17% and a median time to disease progression of 5.4 months compared with values of 20% and 4.7 months in the present study. Although no definition was provided for time to disease progression in the Nordic study to compare it with our own, the results do suggest consistency of efficacy of the XELOX regimen in the second-line setting.

The safety profiles of XELOX and FOLFOX-4 were similar in terms of the toxic effects documented, although there were marked differences in the rates at which some events occurred. FOLFOX-4 was associated with higher rates of neutropenia/granulocytopenia and febrile neutropenia than XELOX, whereas XELOX was associated with higher rates of gastrointestinal toxicity and hand-foot syndrome. These findings are consistent with other direct comparisons of these regimens [9, 13, 20]. Although a similar percentage of XELOX- and FOLFOX-4-treated patients were withdrawn during treatment, adverse events were more commonly cited as the reason for withdrawal in the XELOX treatment group, whereas an insufficient therapeutic response (i.e. disease progression) was more commonly the reason for withdrawal in the FOLFOX-4 group.

In conclusion, XELOX was noninferior to FOLFOX-4 as second-line treatment for patients with metastatic colorectal cancer after prior irinotecan-based chemotherapy.

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references


